IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Byung Sook Moon Martin Jones Johnny Valdez Application No.: 10/672,266 Filed: September 25, 2003 For: LYOPHILIZED BEADS CONTAINING MANNITOL Customer No.: 20350	Confirmation No. 8805 Examiner: Pande, Suchira Technology Center/Art Unit: 1637 DECLARATION UNDER 37 CFR 1.132 BY MARTIN JONES

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Martin Jones, declare as follows:

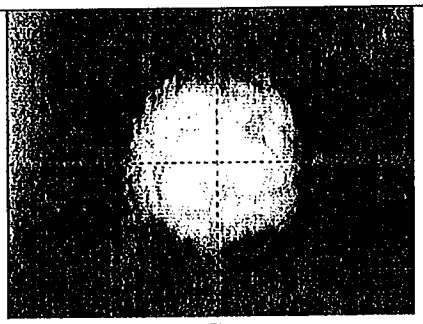
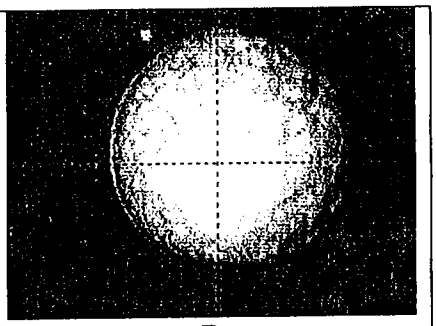
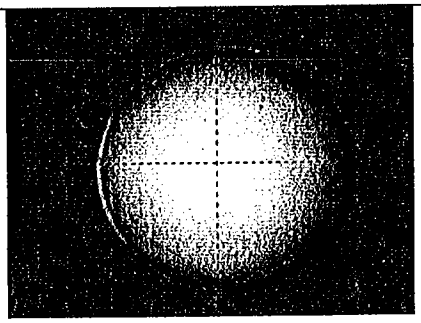
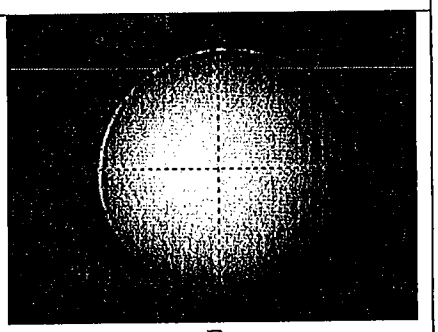
1. I am a Development Manager for Biotechnology at Cepheid in Sunnyvale, CA. I earned a Ph.D. from University of California, Davis, a M.A. from the University of Colorado, Boulder, and a B.S. from George Washington University. Prior to joining Cepheid, I was Director of Chemistry Development at Biex, Inc., a Senior Scientist at Behring Diagnostics, Inc. as well as a Post-Doc at University of California, San Francisco. In addition, I have published more than 10 articles in peer-reviewed scientific journals. My *Curriculum Vitae* is attached as Exhibit 1.

2. I am submitting this declaration to address whether, from an objective point of view, the subject matter of the present application provides surprising results to those working in the art at the time the subject invention was made.

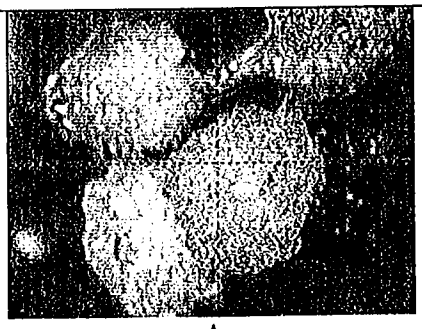
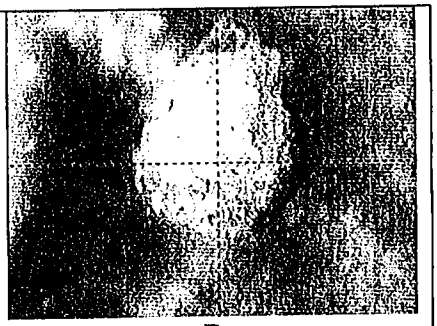
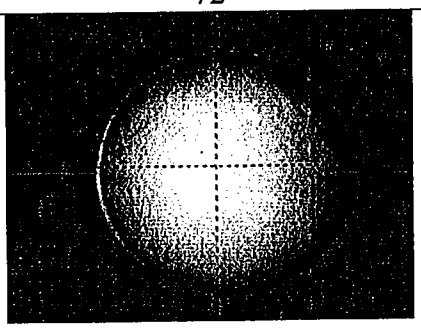
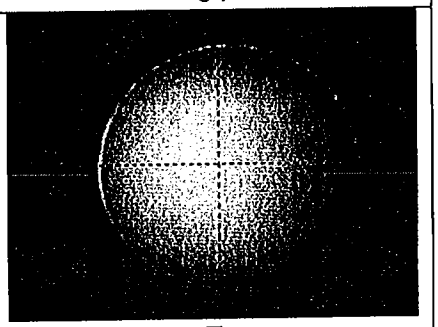
3. I have read and am familiar with the contents of the subject patent application and cited art. I understand that the Examiner has rejected claims 1-8, 10, 12, 45-48, 50, 52 and 53 as allegedly being obvious under 35 U.S.C. § 103(a) over Park, Treml *et al.*, Kellogg *et al.* and Shively *et al.* The Examiner argues that starting from the disclosure of Treml *et al.*, the instant invention would be achieved via routine experimentation.

4. I submit that the instant invention provides surprising results that make the lyophilized beads of the present invention non-obvious over Park and Treml *et al.*

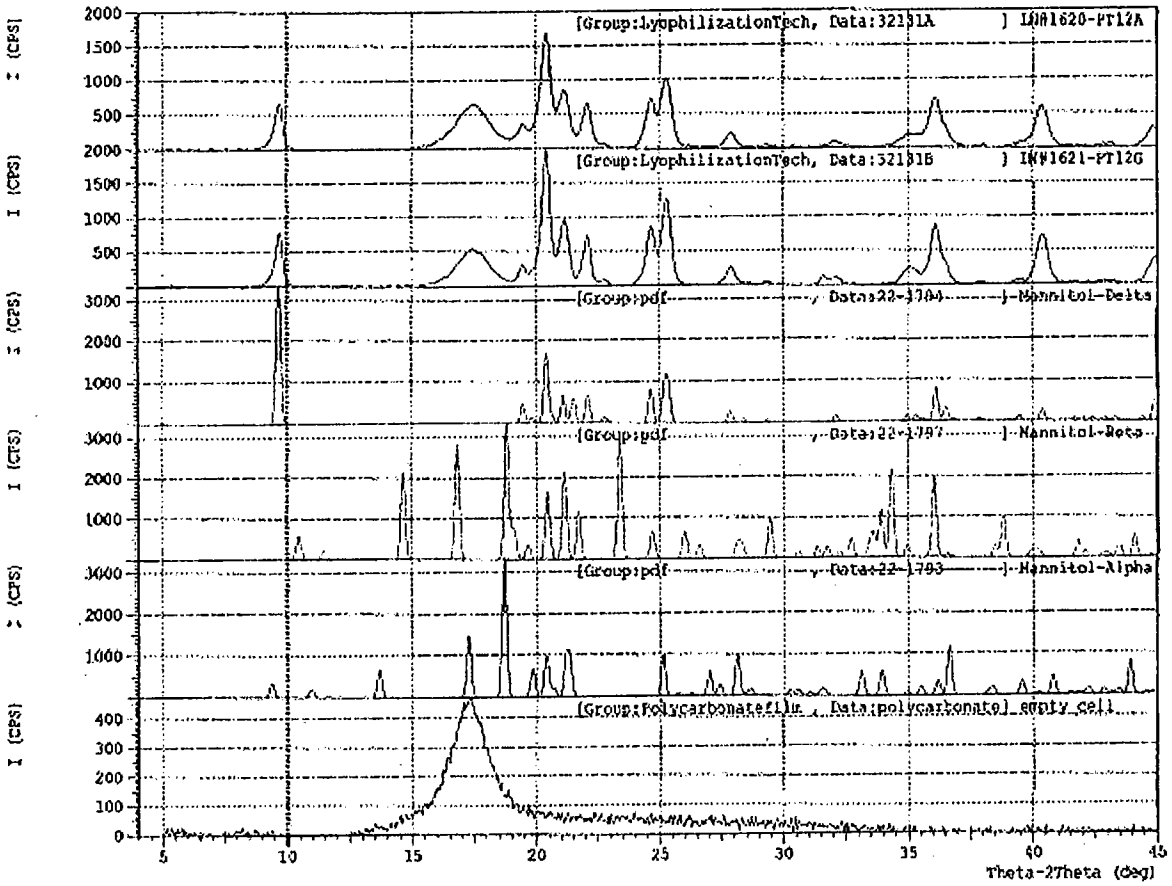
5. The claimed range of between about 53% and about 75% (w/w) of mannitol is a critical range for the lyophilized beads of the present invention. Inside this range, the beads are reproducibly spherical with a smooth morphology. Outside of this range, the beads can be non-spherical, and characterized by a rough surface having pits and protrusions. The pictures below (Figure 1 of the application) demonstrate the surprising advantage of using mannitol in the claimed range of between about 53% and about 75% (w/w). At 43% (w/w) mannitol (C), the bead is semi-spherical, but characterized by sharp protrusions forming a rough surface. At 50% (w/w) mannitol (D), the bead is spherical, but with many pits and craters on the surface (visible as the white spots). At 60% (w/w) mannitol (E), within the claimed range, the beads are spherical and smooth. Beads at 65% (w/w) mannitol (F) are also spherical and smooth. As one of skill in the art, it is surprising that beads having mannitol in the claimed range of between about 53% and about 75% (w/w) are reproducibly spherical with a smooth morphology, as compared to beads having mannitol outside the claimed range.

	 C	 D
Saccharide	Mannitol	Mannitol
% (w/v)	4.5	6.0
% (w/w)	**43**	**50**
	 E	 F
Saccharide	Mannitol	Mannitol
% (w/v)	9.0	11.0
% (w/w)	**60**	**65**

6. The use of mannitol rather than other saccharides or oligosaccharides is also a critical feature of the present invention. The use of mannitol in the claimed range provides beads that are reproducibly spherical with a smooth morphology. The pictures below (Figure 1 of the application) show the effect on bead morphology of using trehalose versus using mannitol. The beads made using mannitol are smooth and spherical (E and F). In contrast, the beads made using trehalose (A and B) form a shiny, clear, irregular shaped mass that adheres to the bottom of the container, even where the % (w/v) of trehalose matches that of mannitol (A versus E). The beads made from trehalose did not lyophilize, and any resemblance to spherical shape by the trehalose beads prior to lyophilization was subsequently lost upon lyophilization. As one of skill in the art, it is also surprising that exchanging mannitol for trehalose at similar % w/v, affords reproducibly spherical beads having a smooth morphology.

	 A	 B
Saccharide	**Trehalose**	**Trehalose**
% (w/v)	9.0	18.8
% (w/w)	72	84
	 E	 F
Saccharide	**Mannitol**	**Mannitol**
% (w/v)	9.0	11.0
% (w/w)	60	65

7. The lyophilized mannitol beads of the present invention, surprisingly, are substantially *crystalline* rather than glassy and amorphous. Lyophilized beads of the prior art are glassy and amorphous, and are thus unable to make the beads of the present invention that are reproducibly spherical with a smooth morphology. Bead crystallinity was assessed using powder x-ray diffraction (PXRD) (see Example 2 of the application). In the figure below, the first two diffractograms are of lyophilized mannitol beads of the present invention. Diffractograms 3, 4 and 5 are diffractograms of the δ, β and α crystal polymorphs of mannitol. The last diffractogram is of an empty cell. The powder x-ray diffractograms for the lyophilized beads of the present invention are consistent with the δ-polymorph of crystalline mannitol. X-ray diffractograms of glassy, amorphous beads demonstrate an amorphous halo with no evidence of crystallinity. Accordingly, the lyophilized mannitol beads of the present invention surprisingly demonstrate a high degree of crystallinity, as compared to other lyophilized beads.



8. The surprising nature of the lyophilized beads of the present invention is also exemplified by the reproducibility and homogeneity of the size of the lyophilized beads. Using three beads from each excipient formulation of Table 1 in the application, bead cross-section was measured using the See-Brez Video Microscope (Quality Control Solutions Inc., Temecula, CA). Each bead was measured twice, for a total of six measurements per excipient formulation. The bead diameter data below (Table 3 in the application) demonstrate that the lyophilized mannitol beads of the present invention have a high degree of uniformity, as determined by the standard deviation (SD) and the coefficient of variation (%CV). The %CV is the ratio of the standard deviation to the mean, and allows comparison of the variation of populations that have significantly different mean values. The trehalose beads have a %CV of around 6.5%, while the lyophilized mannitol beads of the present invention have a %CV of from 0.70 to 2.44, significantly lower than that for the trehalose beads. The higher %CV numbers for the trehalose beads indicate a larger degree of variability and less reproducibility in the diameter of the trehalose beads, as compared to the mannitol beads. Accordingly, the lyophilized mannitol beads of the present invention are surprisingly uniform, as compared to beads with a similar % w/v trehalose.

	Trehalose % w/v		**Mannitol % w/v**					
	18.8	**9.0**	**4.5**	**6.0**	**7.0**	**8.0**	**9.0**	**11.0**
Unit	(mm)	(mm)	(mm)	(mm)	(mm)	(mm)	(mm)	(mm)
Bead #1	2.2890	1.8260	2.1780	2.8190	2.8195	2.9320	2.8671	2.8700
	2.5430	1.7715	2.2020	2.8245	2.7595	2.8635	2.7145	2.8435
Bead #2	2.4470	2.0160	2.1515	2.7605	2.6375	2.8010	2.8365	2.8865
	2.1675	2.0710	2.2170	2.7365	2.7095	2.7840	2.7149	2.8300
Bead #3	2.1875	1.8212	2.2130	2.8835	2.6655	2.8590	2.8265	2.8570
	2.2450	1.7900	2.2315	2.7465	2.7500	2.8585	2.7700	2.8500
Mean	2.31	1.88	2.20	2.80	2.72	2.85	2.79	2.86
SD	0.15	0.13	0.03	0.06	0.07	0.05	0.07	0.02
%CV	**6.50**	**6.77**	**1.33**	**2.04**	**2.44**	**1.84**	**2.33**	**0.70**
N	6	6	6	6	6	6	6	6

9. Given the surprising results above regarding simple changes of saccharide and small changes in the amount of mannitol in the lyophilized bead composition, the lyophilized bead compositions of the present invention are not obvious in view of prior art teachings to beads having similar compositions.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: July 11, 2007

Martin Jones

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